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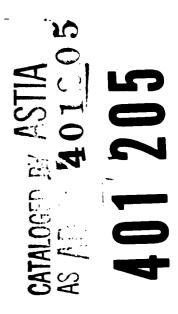
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# TITLE:

PHARMACOLOGICAL STUDY ON CENTRAL SYNAPTIC SYSTEMS AFFECTING MOTOR FUNCTION

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### **OBJECT:**

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To survey a series of compounds with known activity in regard to their actions on synaptic reflexes and the central nervous system.

### INTRODUCTION:

A number of agents are known that are skeletal muscle relaxants. They act by depressing or interrupting transmission of nerve impulses through polysynaptic pathways. Included in this group of compounds are zoxazolamine and mephenesin. These agents also act on brain stem and subcortical areas. They have no direct effect on myoneural junction and in lower concentration, no effect on monosynaptic pathways.

In this study we have examined the muscle relaxant properties of a number of compounds. In addition to their effects on neuro-muscular activity, these substances also have pronounced effects on the central nervous system, as evidenced by increased respiratory rate, changes in temperament, and pupil size. In continuing these studies, we have confined our attention to the CNS effects of one particular substance, Compound No. 6. Attempts have been made to screen possible antagonists. At the present stage of our investigations we have examined the possible antagonistic actions of tetrahydroamino acridine (THA) iproniazid and physostigmine sulfate.

# **METHODS:**

Cats were used in all the experiments and Cpd 6 (0.05 to 1.50 mg/kg) was injected via the femoral vein. THA (3 to 6 mg/kg), physostigmine (0.1 to 1.0 mg/kg) and iproniazid (20 mg/kg) were given I.V. either several days prior to Cpd 6 or in some cases 0.5 to 24 hr after treatment with this agent. The animals were equilibrated for several days on a measured quantity of food. Water was given ad lib.

# RESULTS:

On gross examination, the most outstanding feature found with Cpd 6 (0.1 mgm/kg) was its effects on pupil size (dilation), and food intake. With higher doses (1.5 mgm/kgm) most of the cats exhibited locomotor impairment but this effect only lasted approximately 20 min. Also with this dose respiratory rates were elevated and remained so for periods up to 2 hr. Studies with THA were complicated by actions of the drugs itself. At dose levels in excess of 3 mgm/kgm THA treated cats exhibited extreme rag, aggression, tremors and moderate ataxia. A peculiar type of vociferation was noted in all THA treated cats. On close approach to these animals they emitted a low pitched intermittent 'growl' similar to that of a dog. All these changes could be prevented by pretreatment with Cpd 6.

Since the effects of Cpd 6 on respiration, temperament and locomotor behavior only occur at high dose levels, we have directed our attention to the action of the drugs on pupil size and food intake. These effects occur at low army annual report - page 2 1962-63

dose levels and are relatively easy to quantitate.

## **PUPIL SIZE:**

Pupils of cats given 0.05 mg/kgm of Cpd 6 begin to dilate within 30 min and remain dilated for periods up to 5 to 6 days. Intravenous injection of THA (2 mgm/kgm) or physostigmine (0.1 to 0.8 mgm) immediately after or 24 hr after Cpd 6 had no distinct effects. In a number of animals treated with Cpd 6, physostigmine (1% solution) was applied directly to the left eye. Within a period of 1 hr the pupil returned to the initial size and remained so for a period of 24 hr, at which time the pupil began to dilate again and remained dilated up to 5 to 6 days. Local application of THA was without effect.

# FOOD INTAKE:

Within a 24 hr period following the injection of Cpd 6 (0.05 to 0.10 mg/kg) food consumption of treated cats was markedly inhibited. These data are presented in Fig. 1. In this particular study 15 cats were equilibrated for a period of 8 days. At the end of this time the 24 hr food intake became stable at a level of approximately 190 to 200 gm. At the end of the 8 day period two groups of 5 cats each were injected with 0.05 and 0.10 mg Cpd 6, respectively. From the figure, it can be seen that after 24 hr, food consumption dropped sharply to levels of 10 to 25 gm/24 hr period. A gradual recovery ensued, with food intake reaching normal levels by 72 hr. There was no significant differences between the two dose levels of Cpd 6.

In another series of experiments, the possible antagonistic effects of the monoamine oxidase inhibitor iproniazid (20 mgm/kg/24 hr) were investigated. Twelve cats were again equilibrated for a period of 8 days until food intake became essentially constant (in this group at a level of approximately 175 to 185 gm/24 hr period). At the end of this time iproniazid was given 5 days prior to and 1 day after Cpd 6 (0.05 mgm/kg). It can be noted that iproniazid itself inhibited food intake. At the time Cpd 6 was given, food consumption had dropped to approximately 110 gm/24 hr. After injection of Cpd 6 the typical sharp drop in food intake was noted. The subsequent course of events were not significantly affected by iproniazid, with food consumption reaching pretreatment levels by 72 hr.

Both THA (2 mgm/kg) and physostigmine (1 mg/kg) significantly antagonize the characteristic effects of Cpd 6 on food consumption by cats. Sixteen cats were equilibrated for a period of six days. At the end of this time the cats were split into two groups of 8 cats each and treated two days prior and 1 day after Cpd 6 (0.05 mgm/kg) with daily injections of THA or physostigmine. From data presented in Fig. 3 it can be seen that both drugs inhibit the initial drop in food consumption. THA appears to be more effective than physostigmine at the particular dose levels employed. Food intake returned to pretreatment levels by the end of 36 to 48 hr. These findings should be compared with those summarized in Fig. 1.

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# DISCUSSION:

From what is known of the pharmacology of Cpd 6, it would appear, that the substance is an atropine-like compound acting on acetylcholine mediated synaptic transmission in the CNS. The finding that both THA and physostigmine partially antagonize the effects of Cpd 6 are in keeping with this proposal. Both drugs are known to inhibit cholinesterase.

One of the major problems in finding an effective antagonist to Cpd 6 is that of penetration of the antagonist across the hemo-encephalic barrier to the site of action. Since physostigmine is a tertiary base, we have now decided to investigate a number of tertiary bases which either are acetylcholine-like in action or might be precursors of acetylcholine (HO-CH<sub>2</sub>-CH<sub>2</sub>-N-(CH<sub>3</sub>)<sub>2</sub>). We now have available a number of very stable (to enzyme hydrolysis) tertiary bases of acetylcholine analogs of the general structure

The latter compounds have CNS stimulating activity. During the ensuing year a number of these esters will be analyzed for possible antagonist action.

